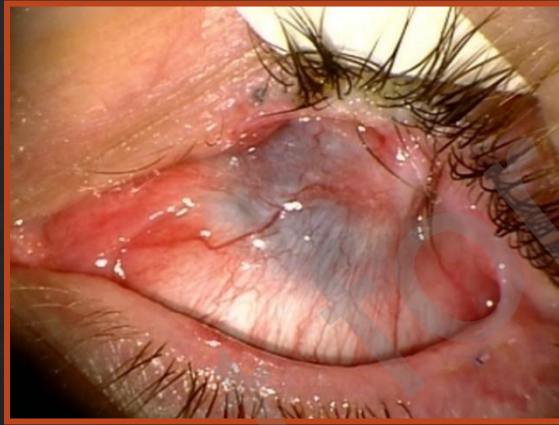


Asia Cornea Foundation Lecture

Management of Severe Ocular Surface Disease: *Lessons Learned*



Edward J. Holland, M.D.

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Professor of Ophthalmology, University of Cincinnati

Financial Disclosures

I have the following financial interests or relationships to disclose:

- ◇ Alcon Laboratories, Inc.
- ◇ Allergan, Inc.
- ◇ Bausch + Lomb, Inc.
- ◇ Katena
- ◇ Kala Pharmaceuticals
- ◇ Mati Pharmaceuticals
- ◇ Mimetogen
- ◇ Omeros
- ◇ PRN
- ◇ TearLab
- ◇ TearScience
- ◇ Senju
- ◇ Shire

Severe Ocular Surface Disease CEI/UC

- **738 eyes** of 432 patients
- Diagnosed at CEI with LSCD between 2002 and 2015
- Mean follow-up of 68 ± 55 months

31% Congenital Aniridia

21% Chemical Injury

17% CL

10% SJS

6% Iatrogenic

4% MGD/Rosacea

2% MMP

2% Unknown

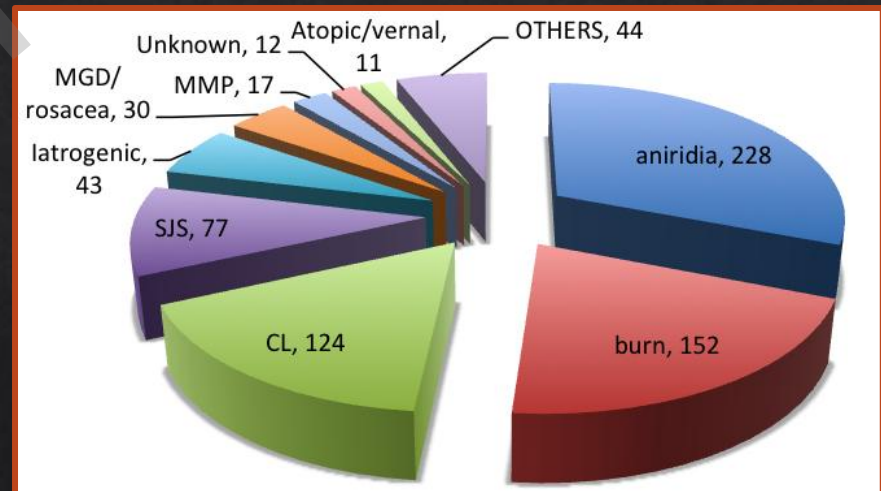
1% Atopic Conjunctivitis

1% Ectrodactyly Ectodermal Displasia (EEC)

1% Poliglandular Autoimmune Syndrome (PGAS)

1% GVHD

<1% Others



Standard Keratoplasty for Severe OSD

93/738 eyes (12.5%) with LSCD had previous Keratoplasty (90 PK – 3 DALK)

All Kertoplasties Failed

14 eyes : Also s/p OSST with insufficient Systemic IS*

- 2 CLAU
- 11 KLAL
- 1 LR CLAL and KLAL

80 eyes : Only Keratoplasty

- 21 Congenital Aniridia
- 25 Chemical Injury
- 3 CL
- 11 SJS
- 10 Iatrogenic
- 2 MMP
- 2 Unknown
- 2 Atopic conjunctivitis
- 2 Poli-glandular Autoimmune Syndrome

* OSST = Ocular surface stem cell transplant
IS = Immunosuppression

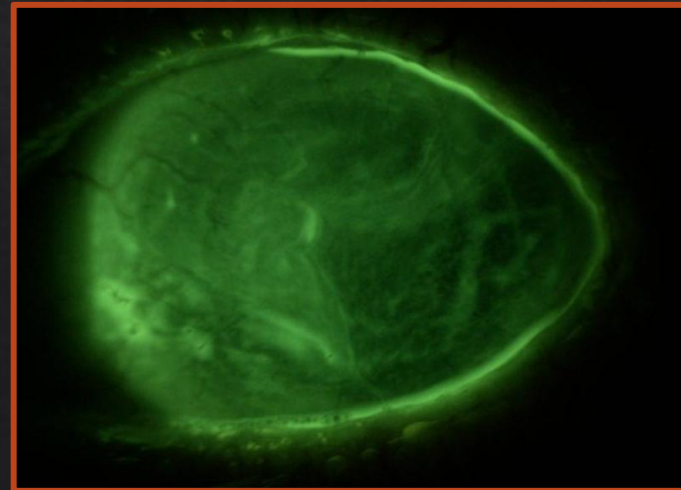
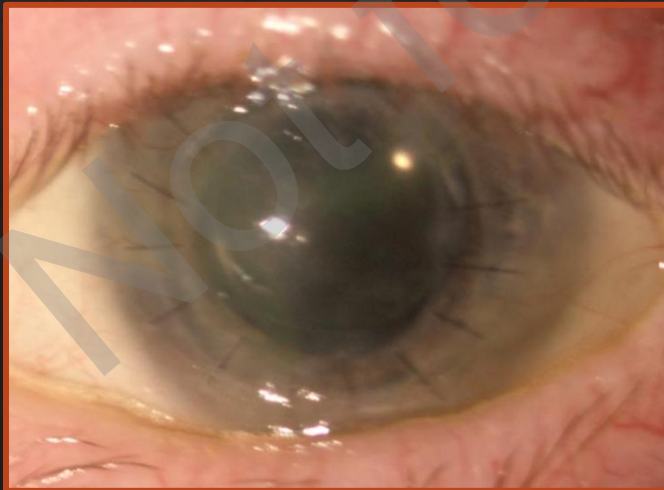


Lesson 1

“Primum non nocere”



- ◆ Do not perform standard keratoplasty without a successful OSST for conjunctival and /or limbal stem cell deficiency
 - All keratoplasties eventually fail

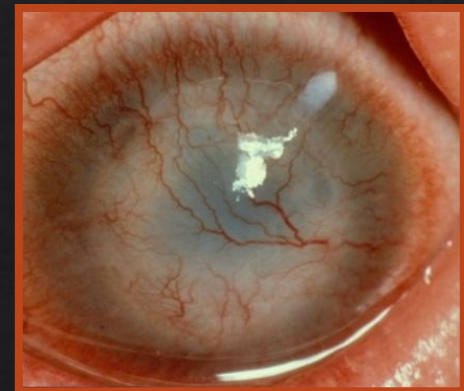
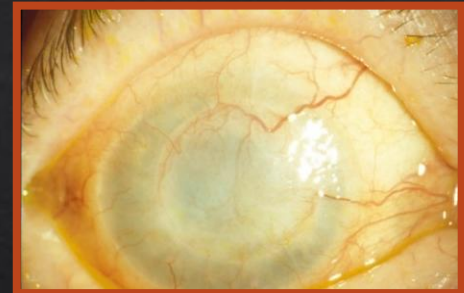
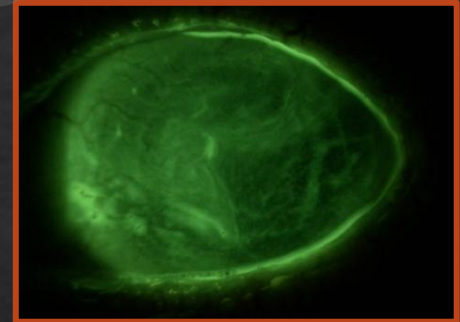


Lesson 1

“Primum non nocere”

Consequences of standard keratoplasty for
Conjunctival or LSCD

- ◇ All keratoplasties eventually fail
 - due to recurrent LSCD
 - subsequent immunologic rejection
- ◇ Patients will then be immunologically sensitized to corneal antigens and have a worse prognosis for OSST



Lesson 2

The Importance of an Ocular Surface Team

Cincinnati Eye Institute / Univ of Cincinnati
Ocular Surface Transplant Team

-Patterned after the Organ Transplantation
Program

◆ **Ophthalmology**

- Cornea- Team Leader
- Oculoplastic, Retina, Glaucoma

◆ **Internal Medicine**

- Organ Tx Immunosuppression Specialist - Nephrologist

◆ **Transplant Coordinator (RN)**

- Patient Education and long term follow up

Lesson 3

Adopt Donor and Recipient Screening and Immunosuppression Protocols from Organ Transplantation

- ◇ Patient monitoring schedules
- ◇ New protocols - Prednisone sparing
 - None or modest doses of Prednisone for < 3 months
- ◇ New Agents
 - Sirolimus (Rapamune)
 - Basiliximab (Simulect)
- ◇ Induction therapy – Intravenous Basiliximab preop
 - Highest risk cases
 - Repeat OS Tx or Penetrating keratoplasties

Evolution of Immunosuppression

	Systemic Regimen	Topical
	None	CsA, prednisolone
1987	Single Drug Prednisone	CsA, prednisolone
1990	Double Drug FK/Pred or CsA/Pred	CsA, prednisolone
2005	Triple Drug FK/MMF/Pred or CsA/Aza/Pred	CsA, prednisolone
2010	Triple Drug with Prednisone sparing FK/MMF/Pred (taper over 3 mos) or CsA/Aza/Pred (taper over 3 mos)	CsA, Difluprednate
Present	Triple Drug with Prednisone sparing Use of Basiliximab and Sirolimus FK/MMF/Pred (taper over 3 mos) or CsA/Aza/Pred (taper over 3 mos)	Lifitigra ^s t, Difluprednate

Systemic meds: FK = Tacrolimus; CsA = Cyclosporine; MMF = Mycophenolate mofetil, Aza = Azathioprine; Pred = Prednisone

Edward J. Holland, M.D.

Perform Complete Donor/Recipient Matching

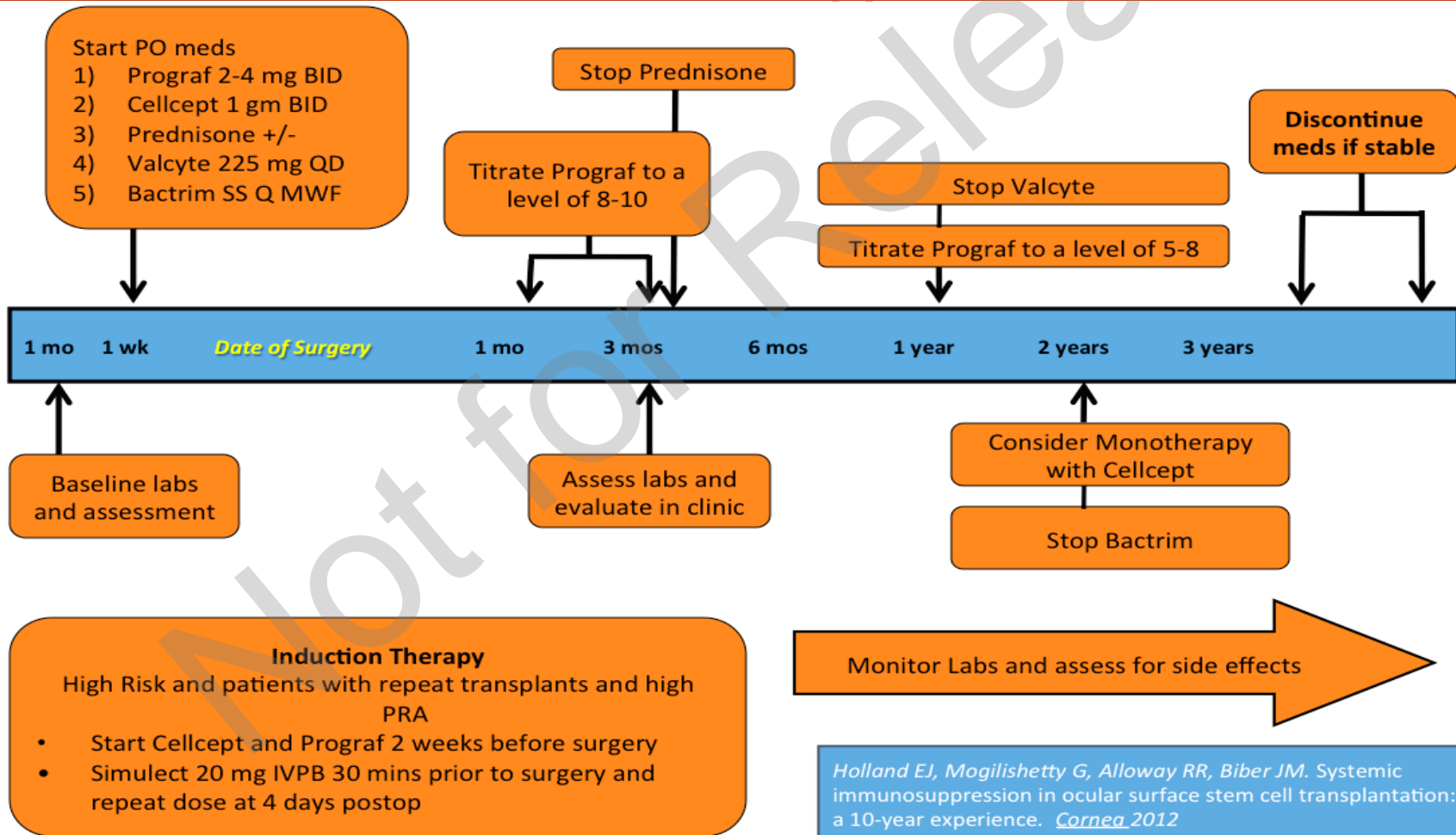
Factors involved in matching

- ◆ Human leukocyte antigens (HLA)
- ◆ Crossmatch
 - Detects recipient antibodies to the potential donor
 - Negative crossmatch is desired
 - Positive crossmatch increases risk of rejection
- ◆ Panel-reactive antibody (PRA)
 - Amount of HLA antibody present in the recipient's serum
 - Higher % PRA makes finding a donor more difficult
- ◆ ABO Blood typing

Individualization of Immunosuppression

Donor Type	Living Donor						Cadaveric Donor		
HLA Type	HLA Identical			Non-HLA match			Does not apply		
PRA %	0	1-50	>50	0	1-50	>50	0	1-50	>50
Induction Therapy	None			None	Simulect 20 mg x 2		None	Simulect 20 mg x 2	
Onset of Meds	Day 0	Day (-7)	Day (-14)	Day (-14)			Day (-14)		
Initial Meds	Prograf/Cellcept/Prednisone			Prograf/Cellcept/Prednisone			Prograf/Cellcept/Prednisone		
Immunosup. Protocol	Prograf taper at 6 mos Cellcept monotherapy at 12 mos			Prograf taper at 12 mos Cellcept monotherapy at 18 mos			Prograf taper at 24 mos Cellcept monotherapy indefinitely		
Repeat Transplant	Yes			Yes, if Donor Specific Antibodies negative			Yes, only if PRA is 0. Prefer KPro vs. LR-CLAL		

CEI/UC Systemic Immunosuppression Protocol



Lesson 4

Immunosuppression in OSST is Safe

Adverse Effects Study

◆ Methods

- Retrospective study over last 10 years
- All patients undergoing OSST and receiving concomitant IS from 2000-2007

◆ Results

- 136 patients (225 eyes)
- Mean follow-up after OSST was 4.5 yrs (+/- 2.7 yrs)
- 76 patients (56%) had no systemic co-morbidities at initial presentation
- Mean duration of IS was 3.5 yrs

Immunosuppression Adverse Effects Study

Results

- ◇ 105 patients (77.2%) stable ocular surface at last visit
- ◇ 37 patients (35.2%) with a stable ocular surface were able to be tapered successfully off IS
- ◇ Majority of patients remaining on IS were on monotherapy (Cellcept)
- ◇ Adverse events:
 - **No deaths, No secondary tumors**
 - 3 severe events in 2 patients (MI, PE)
 - 21 minor events in 19 patients (14% - transient ↑ Cr, HTN, PTDM, pneumonia, ↑ liver enzymes, AVN of hip)

Systemic Immunosuppression: A 20-year Experience

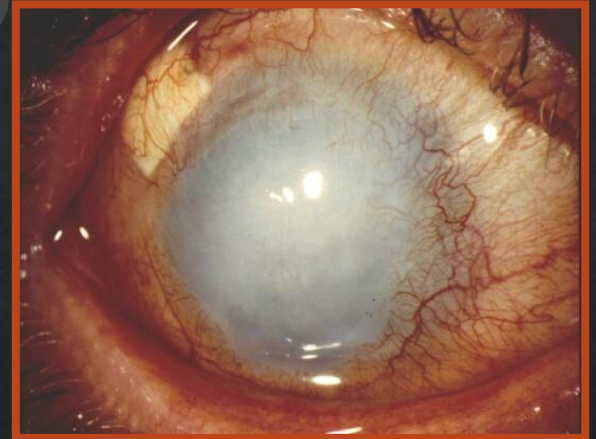
- ◇ 270 patients followed while on systemic immunosuppression
- ◇ 375 eyes underwent OSST
- ◇ No deaths
- ◇ Minimal severe adverse events
 - Secondary tumors: 1 SCC, 1 melanoma in KLAL
 - 0 CVA, 2 MI, 1 PE

Lesson 5

“Staged Management” Results in Better Outcomes

1. Glaucoma aggressively treated

- ◇ Early placement of tube shunts
- ◇ Topical glaucoma meds toxic to surface



2. Lid abnormalities corrected

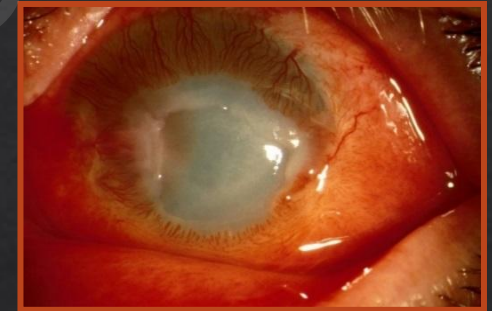
- ◇ Surgical correction of entropion, trichiasis & exposure



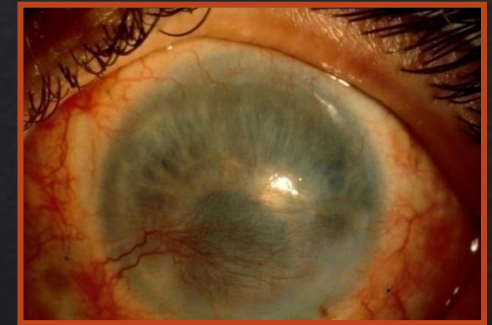
Severe Ocular Surface Disease “Staged Management”

3. Ocular Surface inflammation suppressed

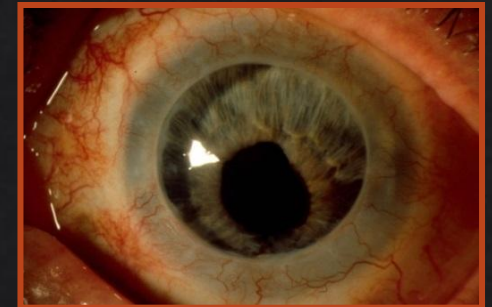
- ◆ Topical and systemic immunosuppression



4. Ocular Surface Stem Cell Transplantation or KPro

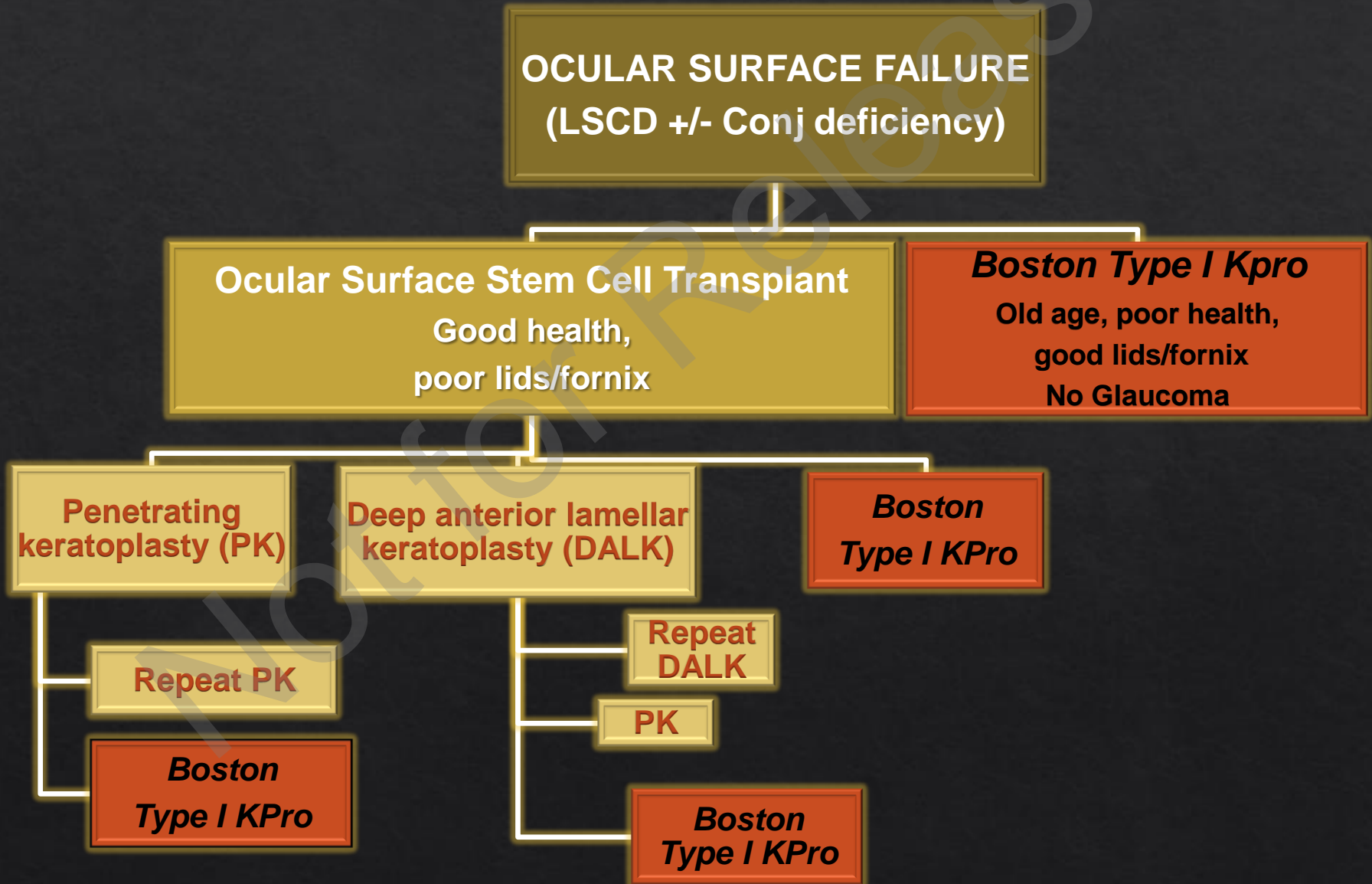


5. Penetrating or Lamellar Keratoplasty or KPro



Lesson 6

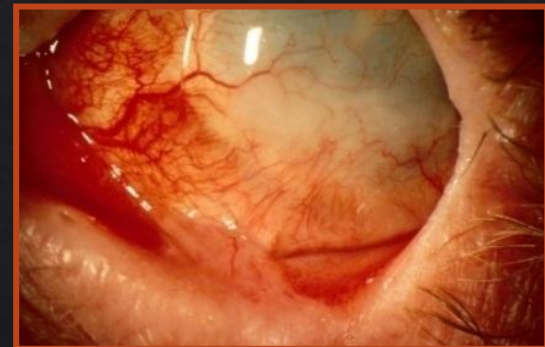
Develop a Treatment Paradigm



Treatment paradigm is Based on Staging of Disease Severity

Factors

- ◆ Age of recipient
- ◆ Medical status of recipient
- ◆ Level of inflammation
- ◆ Status of the Conjunctiva
- ◆ Previous corneal or SC surgery
- ◆ Level of Match with LR tissue



Ocular Surface Stem Cell Transplantation Techniques

◆ Conjunctival Limbal Autograft

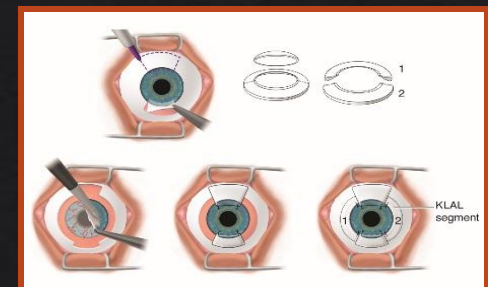
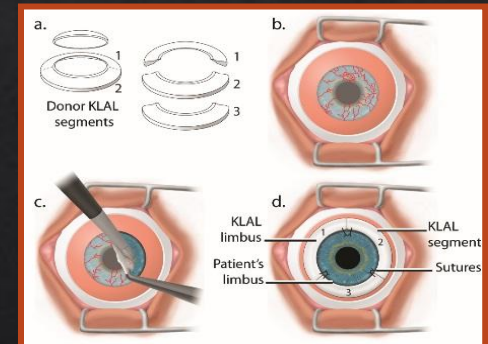
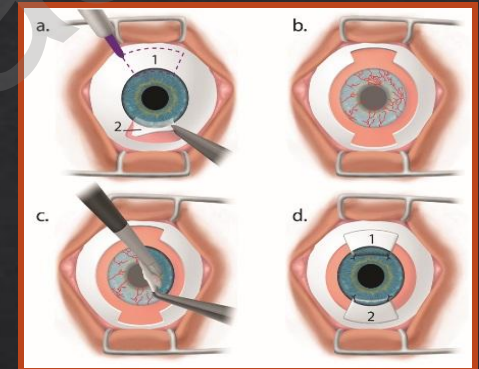
- *Donor – Fellow Eye*

◆ Living-related conjunctival limbal allograft

- *Donor – Relative*

◆ Keratolimbal allograft

- *Donor – Cadaver*

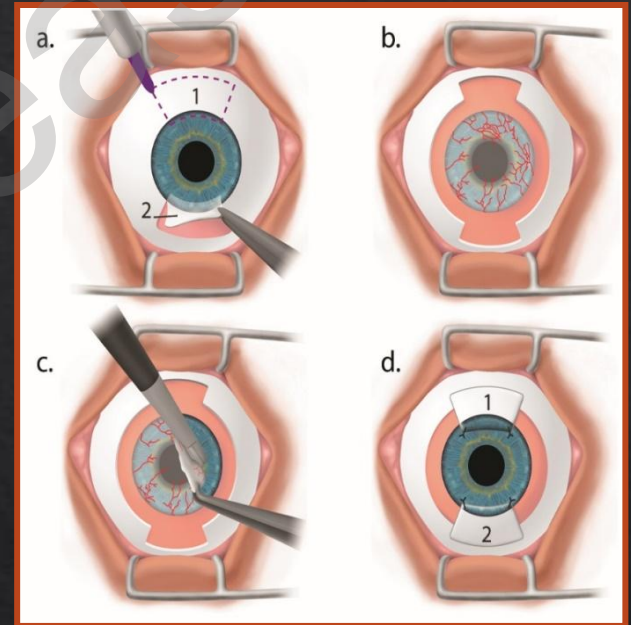


Ocular Surface Trauma

Unilateral Injury

Conjunctival Limbal Autograft

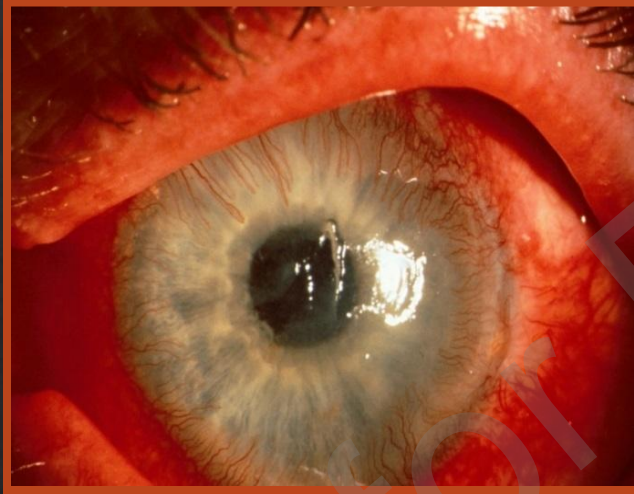
- ◇ Procedure of choice
- ◇ Eliminates rejection
- ◇ Need the fellow eye to have normal conjunctiva and limbus
 - No history of long term CL wear
- ◇ Only have one chance for fellow eye to be donor



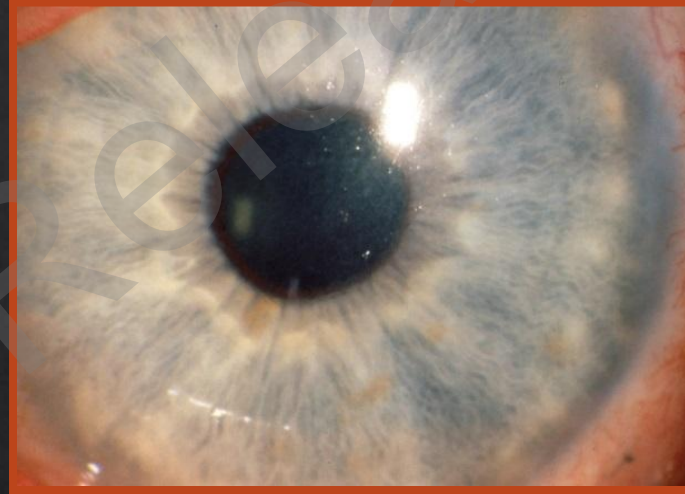
Conjunctival Limbal Autograft – CLAU

1990

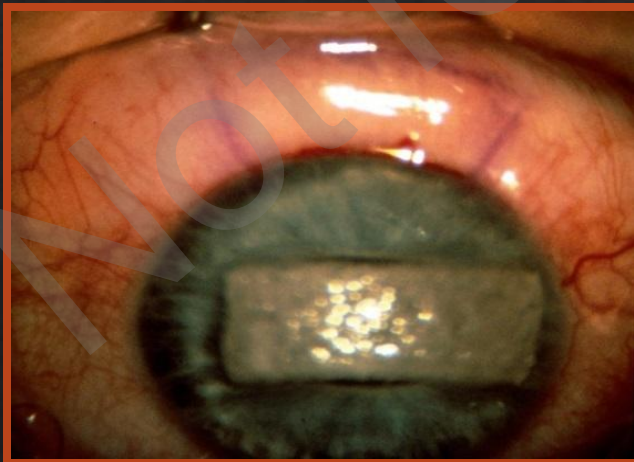
Pre Op
Alkali
injury



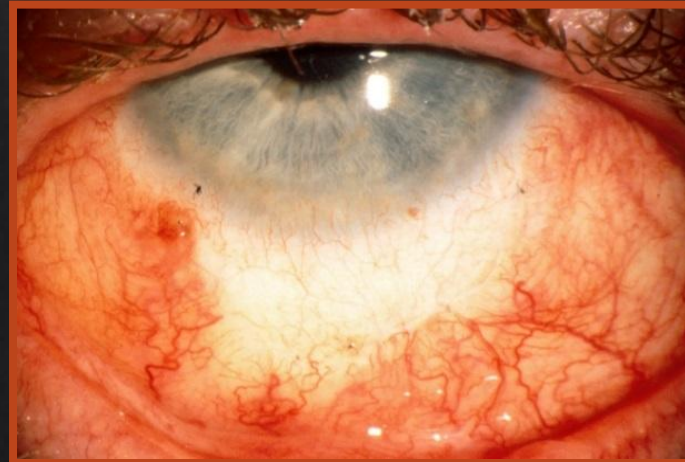
Post Op
Cornea



Donor
Fellow
Eye



Post Op
Graft



Conjunctival Limbal Autograft (CLAU)

Donor Eyes:

49 CLAU procedures performed from 2006 -2016

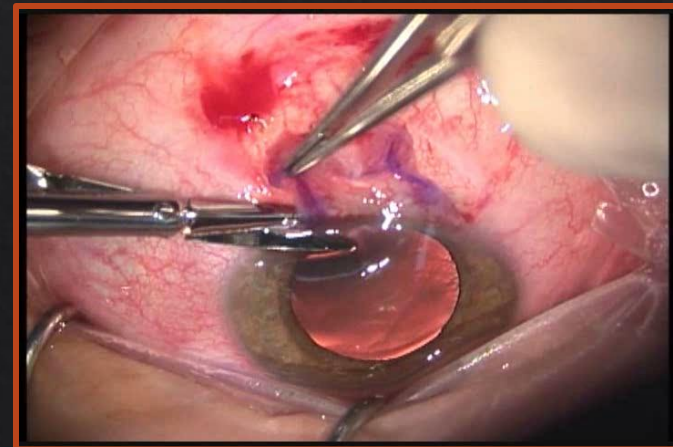
◇ 28 CLAU, 19 CLAU/KLAL, 2 CLAU/LR-CLAL

◇ All donor eyes had a stable ocular surface at last f/u

◇ Followed for mean 36.8 months

◇ Mean preoperative BCVA (20/24)

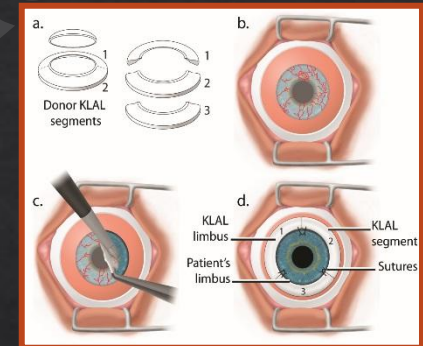
◇ Mean postoperative BCVA (20/22)



Ocular Surface Transplantation for Bilateral Disease

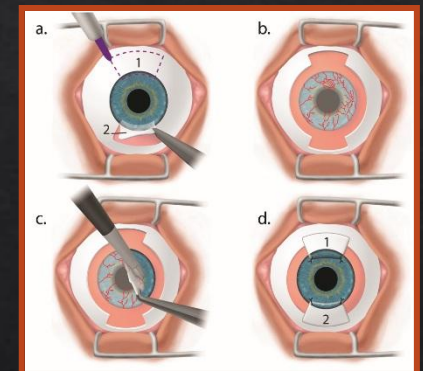
◆ Keratolimbal allograft

- *Donor – Cadaver*



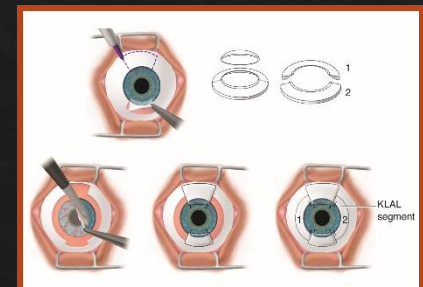
◆ Living-related conjunctival limbal allograft

- *Donor – Relative*



◆ Combined LR-CLAL/KLAL

- *Donor – Relative and Cadaver*



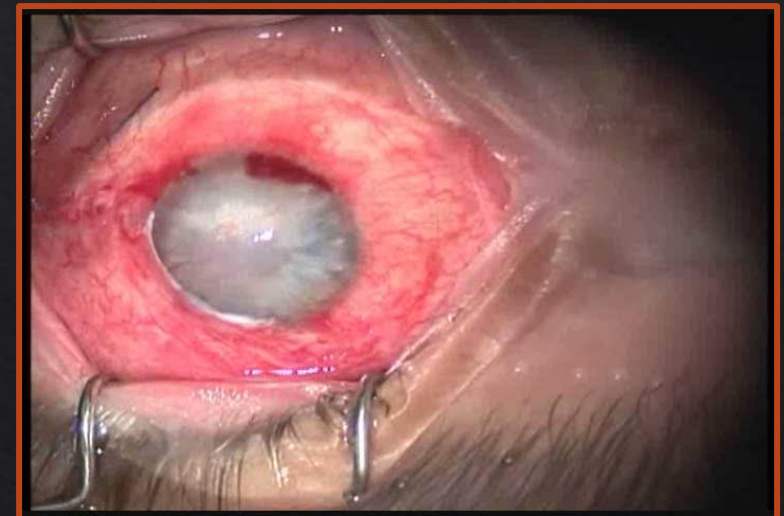
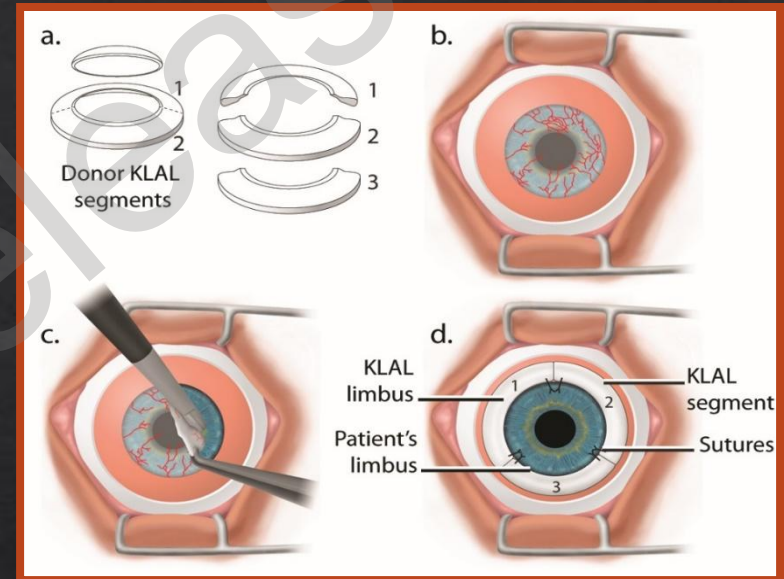
Keratolimbal Allograft - KLAL

Advantages

- ◇ One Procedure
- ◇ Does not involve a living donor
- ◇ Excellent number of Stem Cells

Disadvantages

- ◇ No tissue Typing
- ◇ Increased risk of rejection
- ◇ No source of conjunctiva



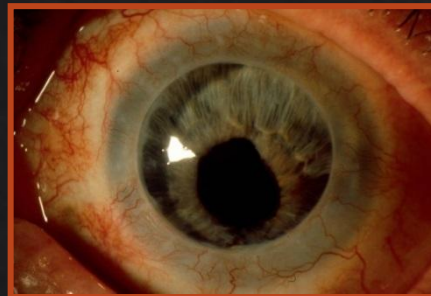
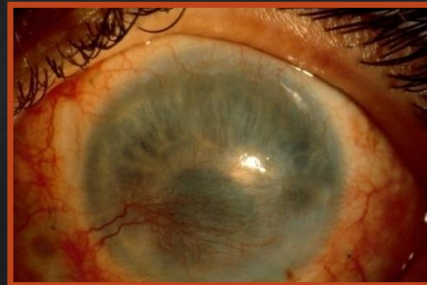
KLAL for Severe Ocular Surface Disease

- ◇ Alkali Injury
 - Pre Op

◇ S/P KLAL

◇ S/P Penetrating Keratoplasty

PreOp Va = HM PostOp Va = 20/30	PreOp Va = HM PostOp Va = 20/25
------------------------------------	------------------------------------



20 y/o Male with Congenital Aniridia

Findings

◇ Vision

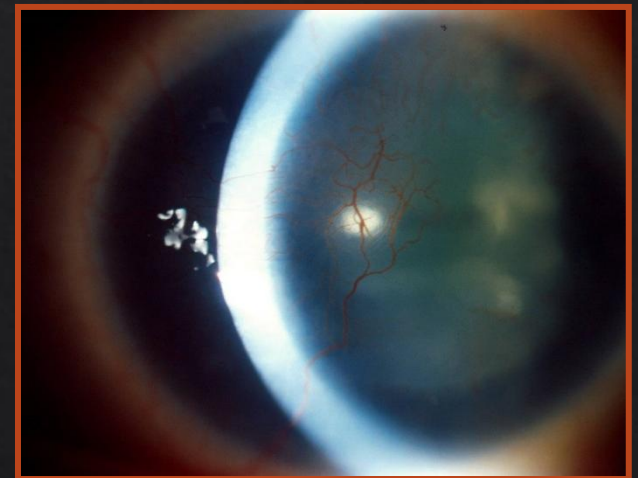
- 20/400 OD
- CF OS

◇ Cornea

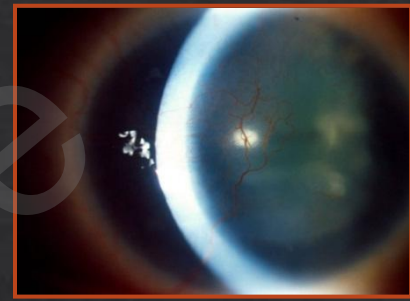
- Total corneal pannus with epithelial haze and NV
- Anterior Stromal Scarring

◇ Lens

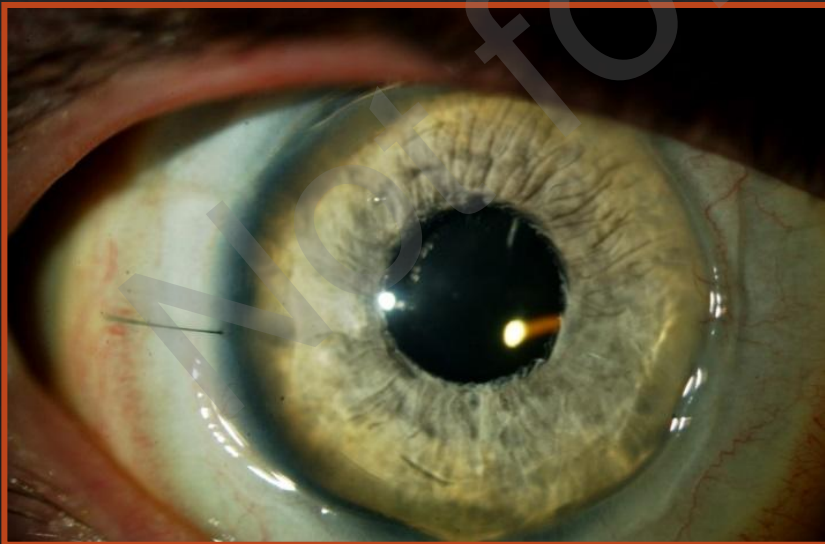
- Cataracts
- Superior subluxation



20 y/o Male with Congenital Aniridia



- ◇ S/P Phaco with CTR and Human Optics Artificial Iris
- ◇ Subsequent KLAL OU
- ◇ Va 20/80 OU (macular hypoplasia) 8 years post op

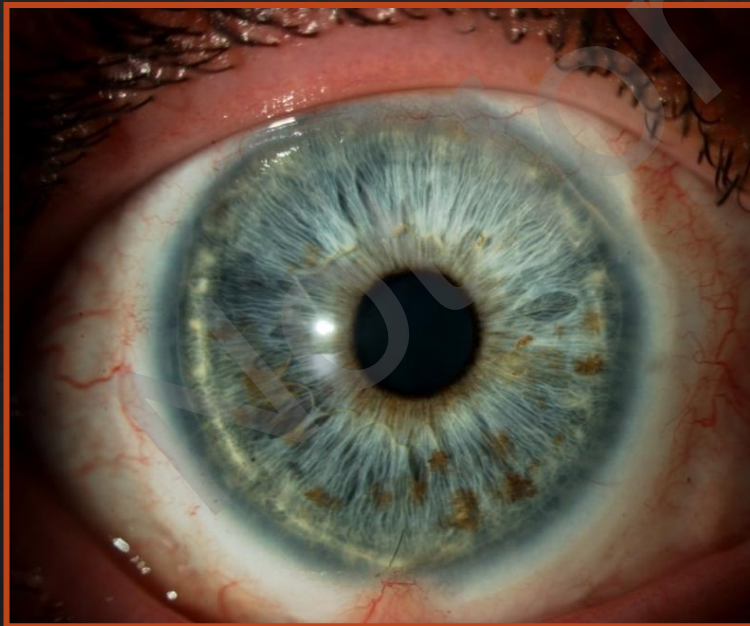


Keratolimbal Allograft for Variant Aniridia

Pre Op 20/400

12 years (and 2 children) Post-op

20/25 and 20/40



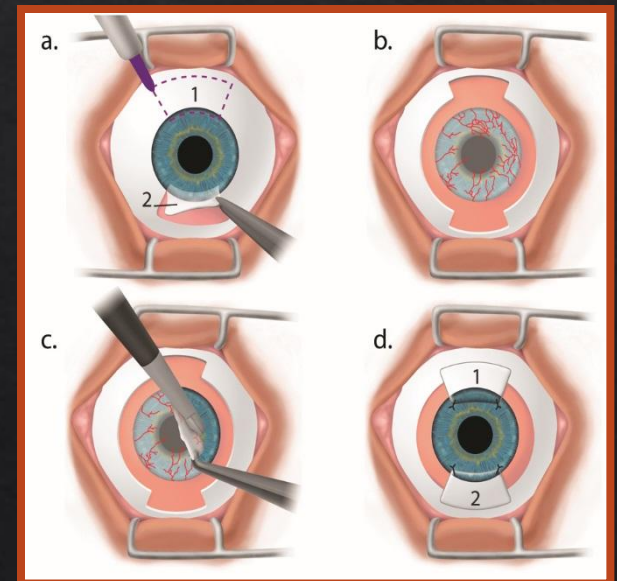
Living Related Conjunctival Limbal Allograft LR- CLAL

Advantages

- ◇ Supplies conjunctiva and limbal SCs
- ◇ Need good HLA match
- ◇ Need the donor eye to have normal conjunctiva and limbus
 - No history of long term CL wear

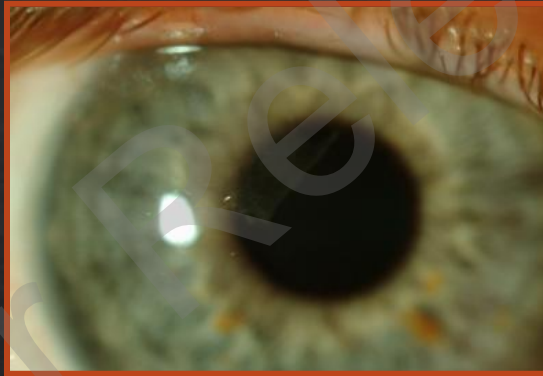
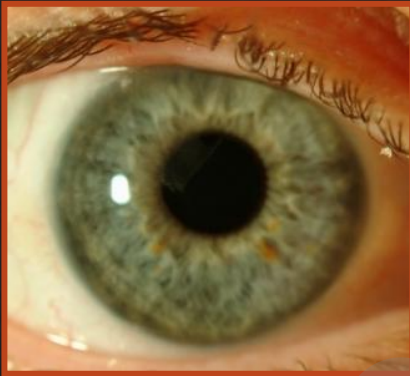
Disadvantages

- ◇ Two procedures
- ◇ Risk to donor
- ◇ Does not supply 360 degrees of

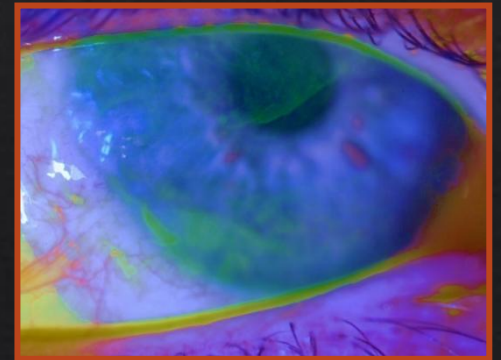
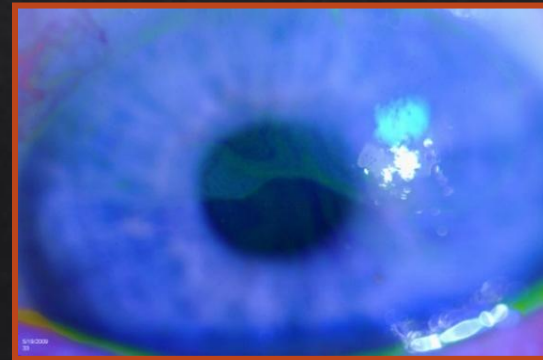


48 Y/O SCLWear x 25 Years
Tx with Super K and AMT x 3

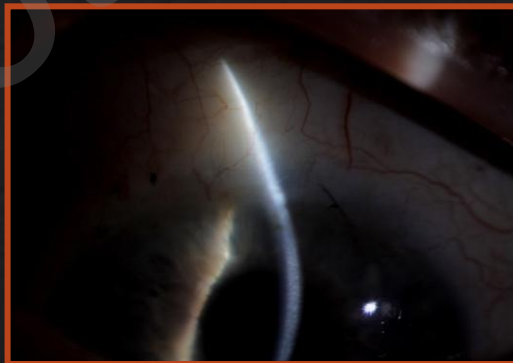
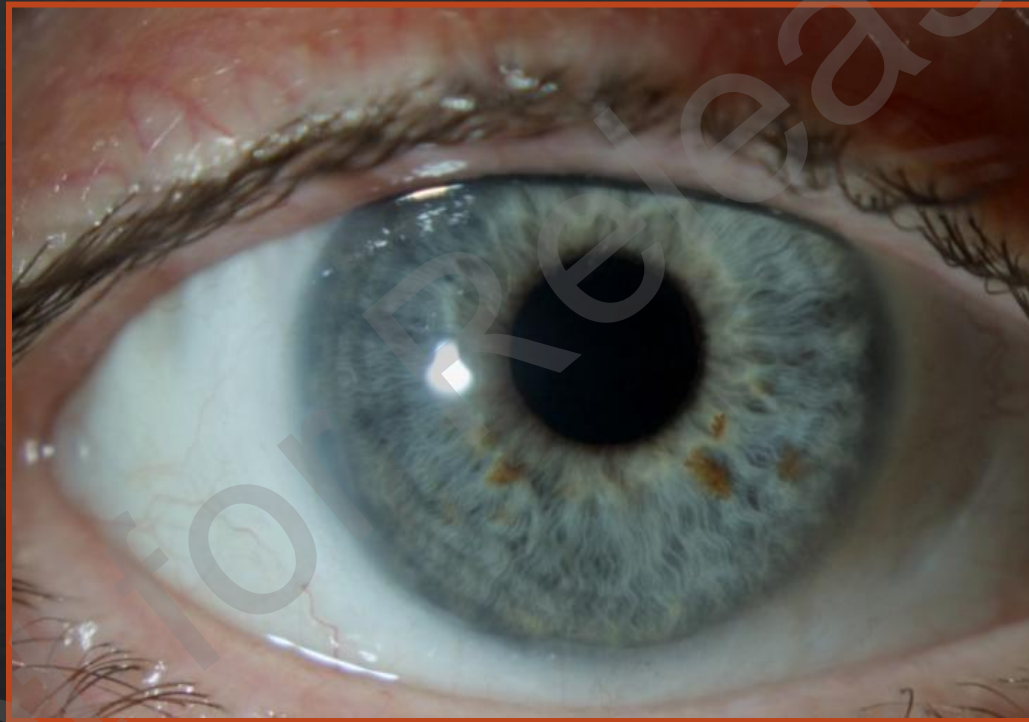
2007



2008

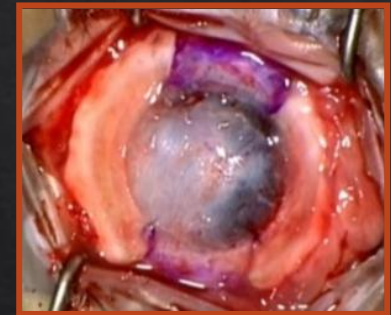
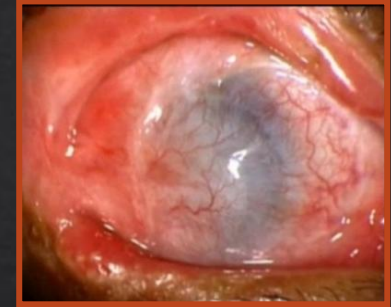


10 Yrs S/P LR-CLAL
Va 20/20 OU



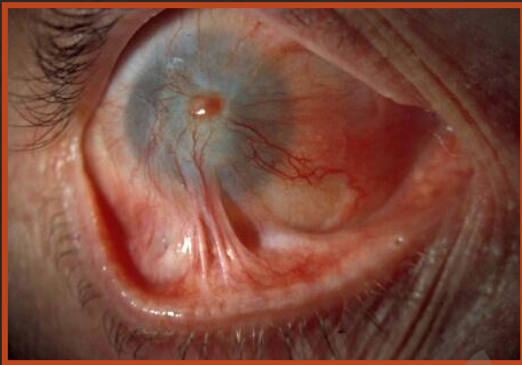
The “Cincinnati Procedure” Combined LR-CLAL/KLAL

- ◇ Recipient limbus surrounded 360°
- ◇ Addresses both severe conjunctival & limbal stem cell deficiency
- ◇ Provides conjunctiva and limbal stem cells: goblet cells, mucin, surface stability, better environment for keratoplasty



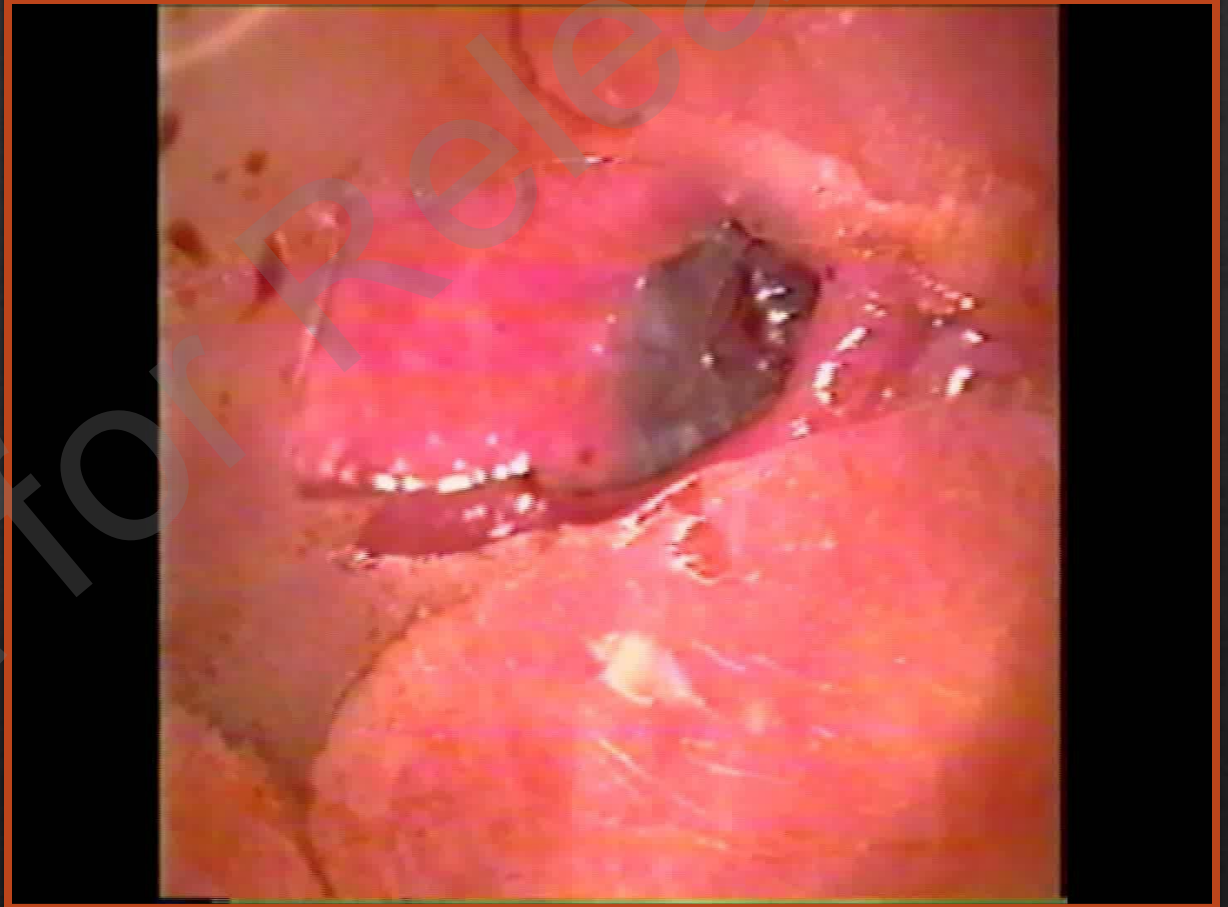
Alkali Injury with Severe LSCD and Conjunctival Deficiency

S/P 4 Keratoplasties



Stevens-Johnson Syndrome

Severe Ankyloblepharon



Lesson 7

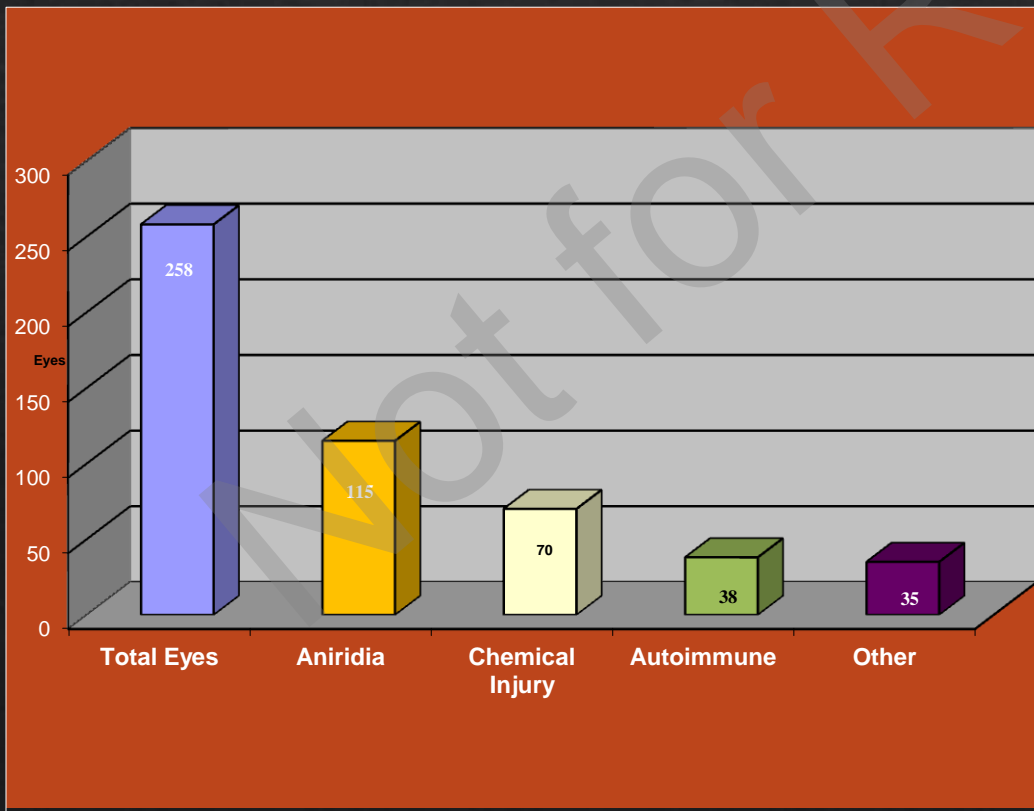
We can achieve good long term outcomes with OSST for bilateral severe ocular surface disease

CEI/ UC OSTx Patients

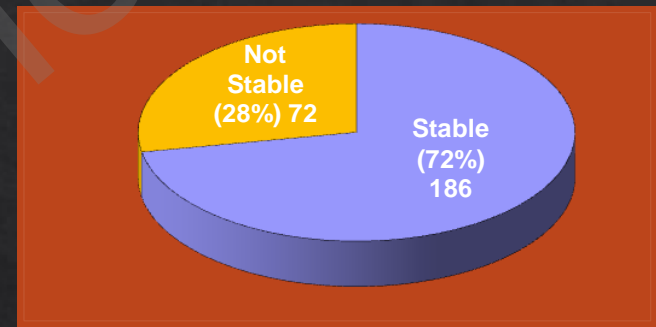
N = 258 Eyes

125 with Severe Conjunctival Disease

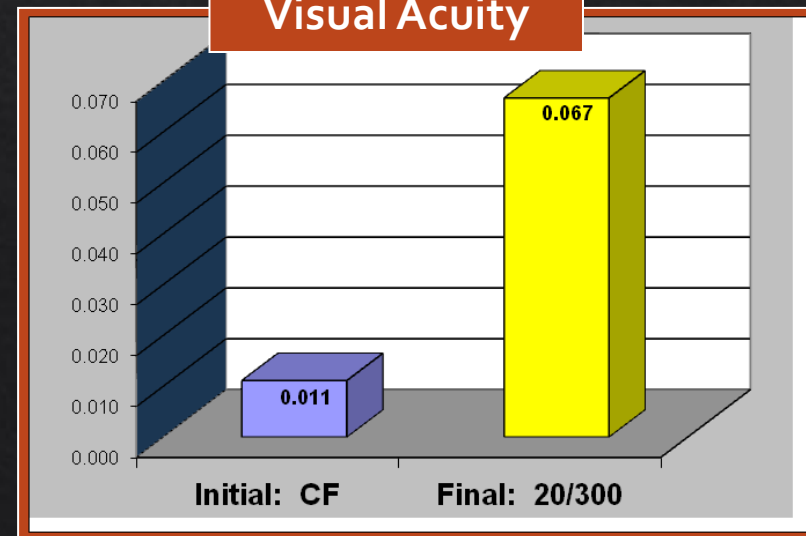
Mean F/U = 5 years



Ocular Surface Stability



Visual Acuity

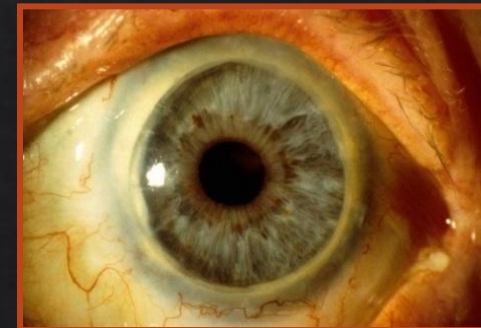


OSST Long Term Study

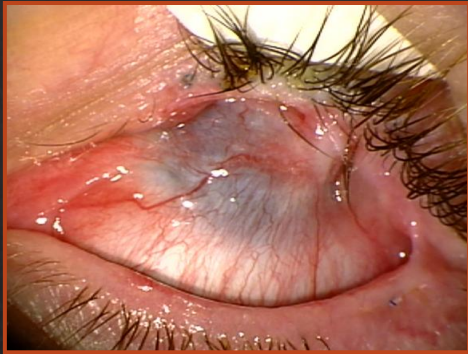
- To assess the long term outcome of OSST
- Inclusion criteria:
 - Clinically established total limbal stem cell deficiency
 - Minimum follow up of 5 years after OSST
- Results
 - Mean f/u duration: 9 years \pm 35.7 mos
 - Patients: 110 patients and 165 eyes

OSST Long Term Study

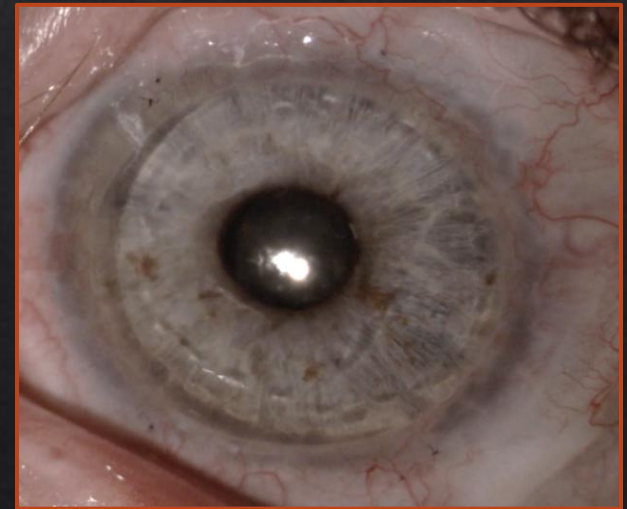
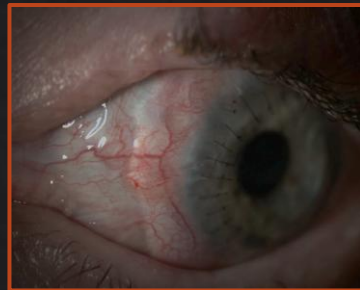
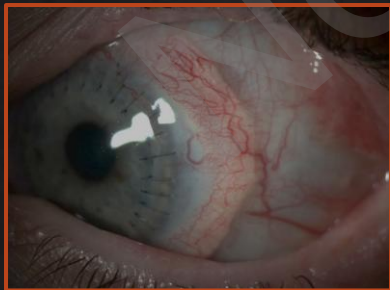
- Ocular surface stability was achieved in 73%
- Comparing pre-op VA and VA at the last f/u:
 - 62% had 2 lines or more improved VA
 - 8% no change in VA
 - 19% worse VA
- 53 eyes with 10 or more years follow up
 - 32/53 eyes (60%) had consistently maintained a stable ocular Surface
 - Long survival group had:
 - 64% completely tapered off IS, majority of others on low dose Cellcept
 - No irreversible Adverse SEs from IS
 - **Compliance rate of 93%** (only 2 non-compliant)



The "Cincinnati Procedure" Combined LR-CLAU/KLAL



2 years
post op

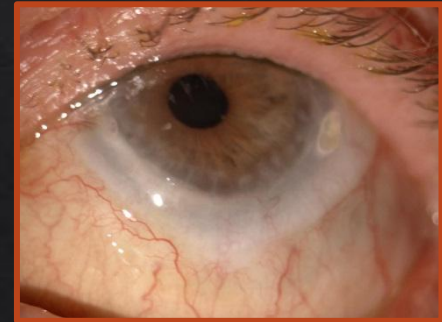
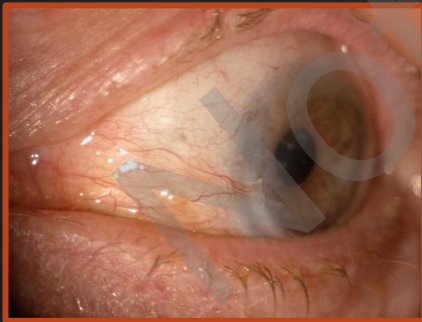
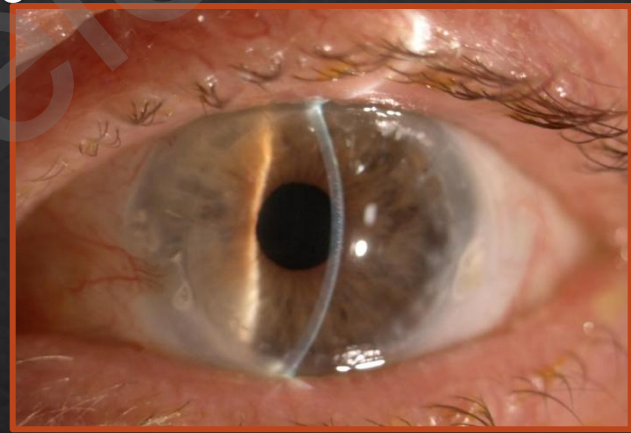
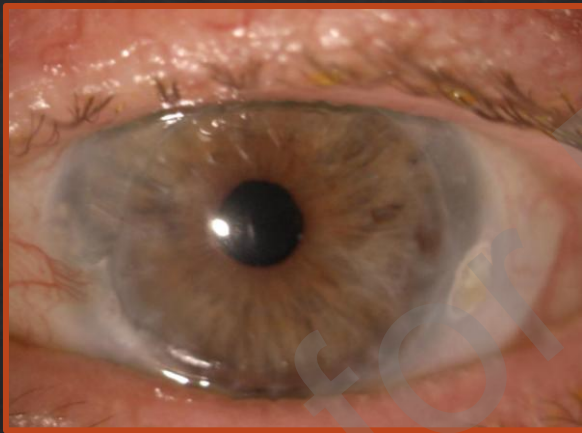


8 years post op
20/30

Keratolimbal Allograft and subsequent PK for Chemical Injury

16 years post-op

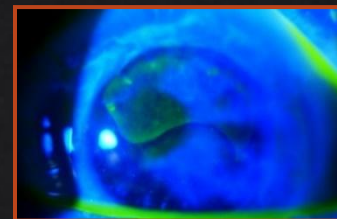
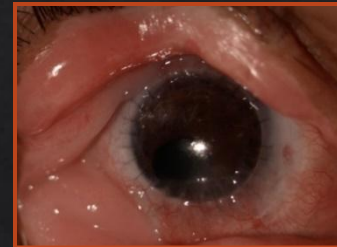
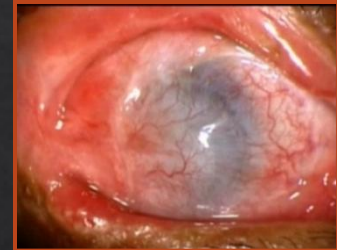
20/40



Lesson 8

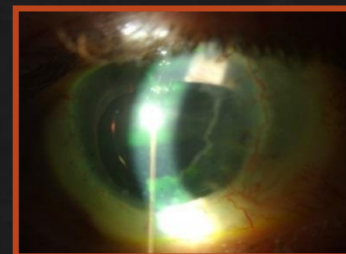
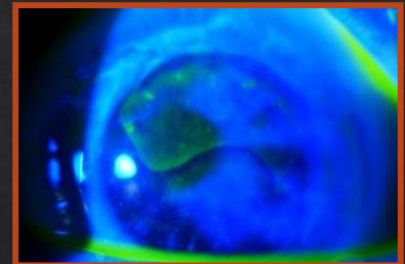
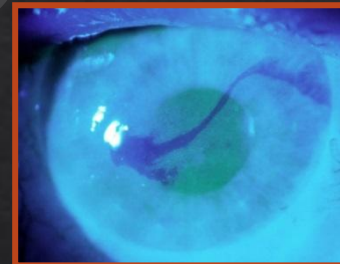
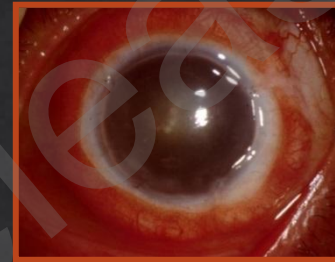
OSST requires close monitoring and may have significant complications

- ◇ Multiple surgeries often needed
- ◇ Risk of Glaucoma
- ◇ Complications of Severe Dry Eye
- ◇ Healthy ocular surface needed for good vision
- ◇ Immunosuppression required
 - Close medical monitoring
 - Risk of side effects



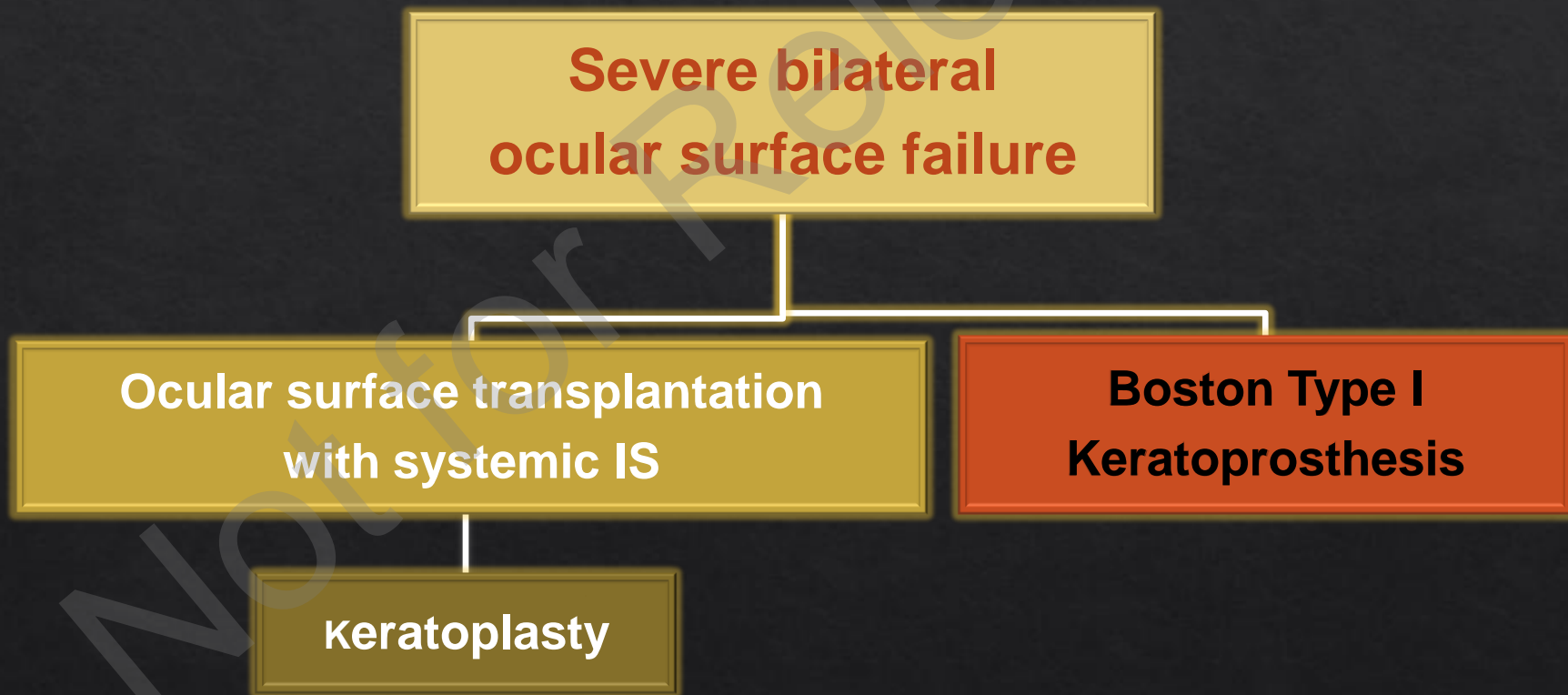
Ocular Surface Tx Complications

- ◇ OST surface failure
 - Immunologic: acute or chronic rejection, late failure, stem cell exhaustion
 - Non-immunologic: lid abnormalities, mucin &/or aqueous deficiency
- ◇ Keratoplasty failure
 - Immunologic: epithelial, subepithelial, stromal, endothelial
 - Infectious keratitis



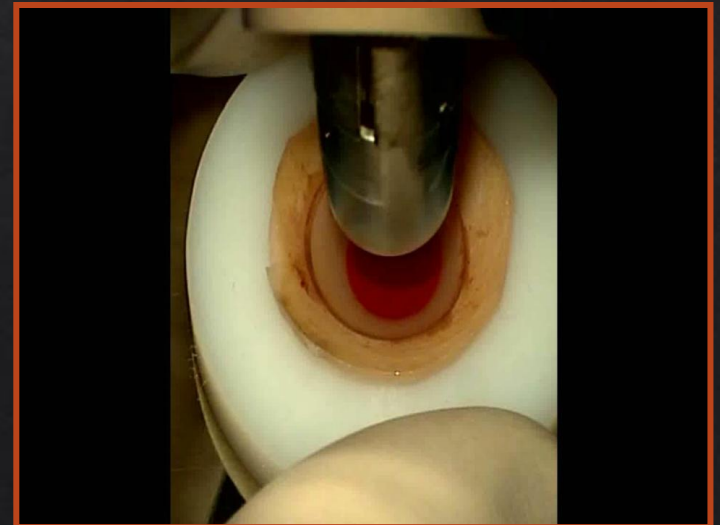
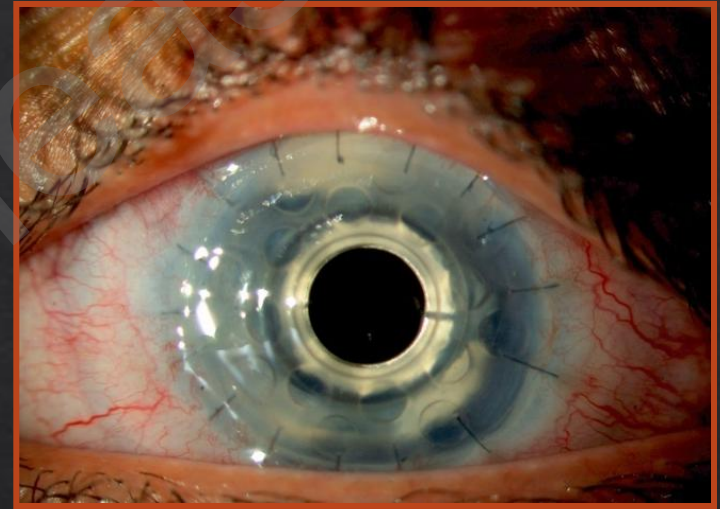
Lesson 9

Incorporate Keratoprosthesis Surgery into the Treatment Paradigm



Boston Type I KPro Advantages

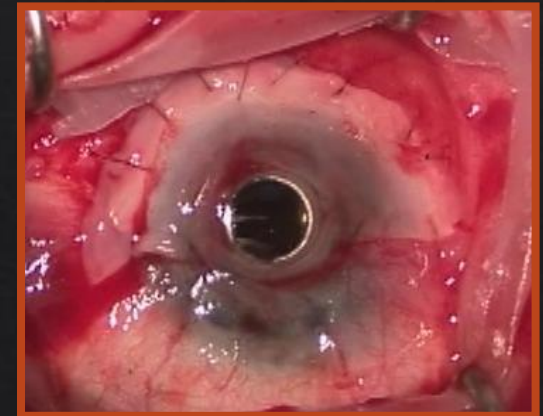
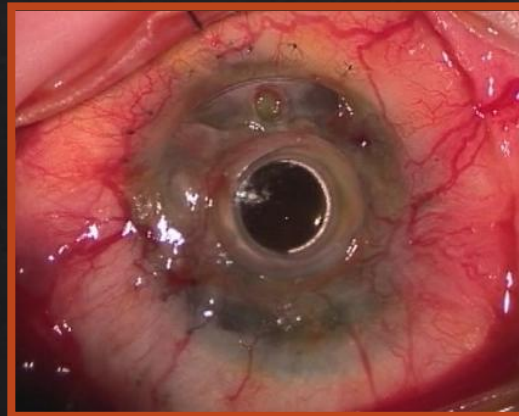
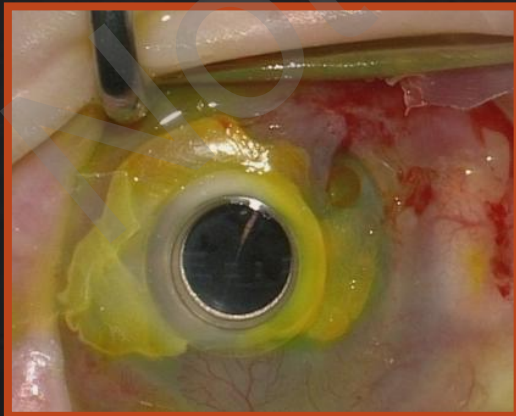
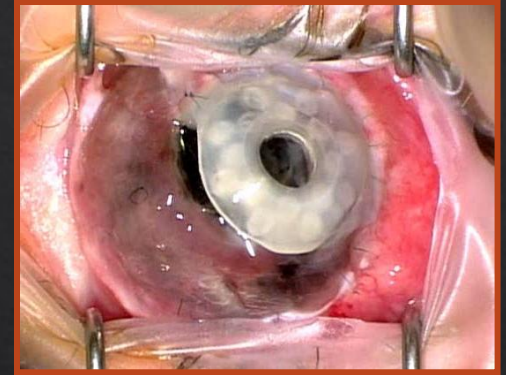
- ◆ Single operation (no staged keratoplasty required)
- ◆ Technically similar to PK surgery
- ◆ No immunosuppression
- ◆ No risk of rejection
- ◆ Poor ocular surface does not interfere with vision



Lesson 10

Boston KPros have Complications

- ◆ Inability to measure IOP accurately
- ◆ Lifelong close follow-up
- ◆ Lifelong topical antibiotics
- ◆ Complications can lead to loss of eye
 - Corneal melts, infectious keratitis, endophthalmitis
- ◆ Caution in severe dry eye, ↑ risk of melt (8-17%)



Boston Type I KPro Glaucoma

Glaucoma Complications	CEI Study (1) N = 128 eyes Mean f/u = 31.7 mos	UC Davis study (2) N = 40 eyes Mean f/u = 33.6 mos
Development of glaucoma after KPro	3.1%	27.5%
Progression of glaucoma	21.1%	22.5%
Tube erosion	13.3%	22.5%
Glaucoma causing loss of BCVA	47% lost ≥ 2 lines of BCVA over f/u	54% of eyes did not retain BCVA $\geq 20/200$ after ≥ 1 year f/u

1. Ang AY, Holland EJ, et al. Long-term outcomes and complications of the Boston type 1 keratoprosthesis. ASCRS, 2012.
2. Greiner MA, Mannis MJ, et al. Longer-Term Vision Outcomes and Complications with the Boston KPro Ophthalmol 2011.

CEI/UC Boston KPro Study Complication Rate Worse in OSD



N = 126	Rate	Pre-operative diagnoses
Corneal Melts	19/26 (15.1%)	12/19 (63%) had Severe OSD*
Infectious Keratitis	10/126 (7.9%)	9/10 (90%) had Severe OSD
Endophthalmitis	3/126 (2.4%)	2/3 (67%) had Severe OSD

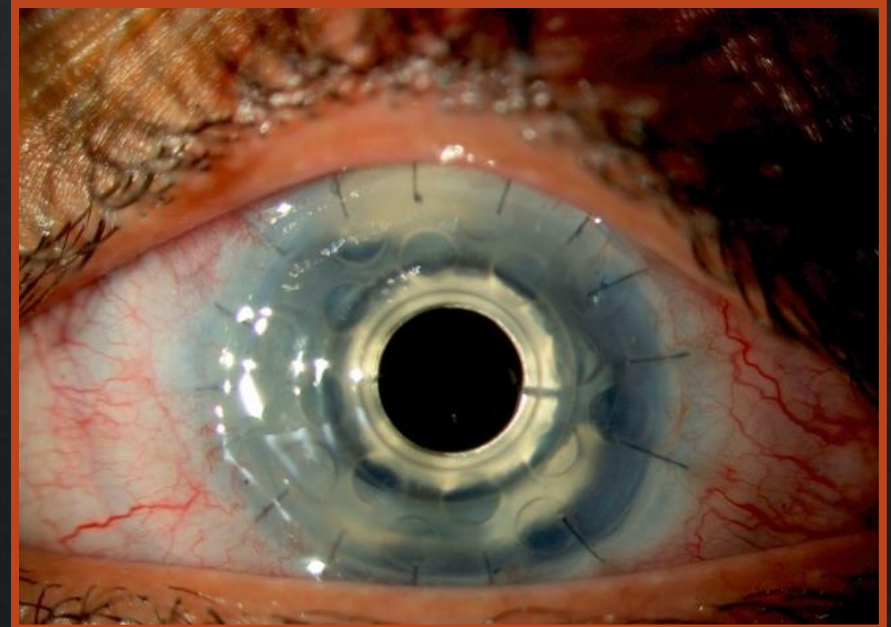
*Severe OSD = SJS, OCP, chemical injuries

Ocular surface reconstruction

*Ocular Surface Stem Cell
Transplantation*

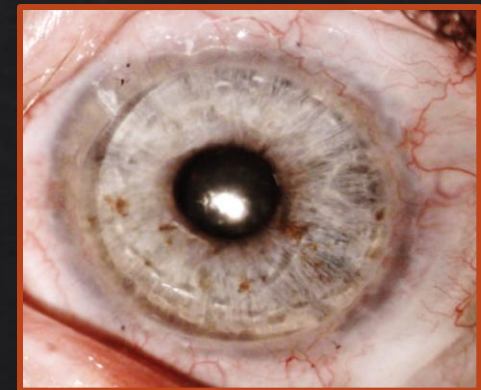
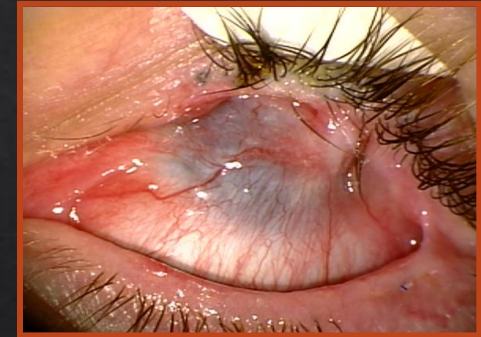
vs.

Keratoprosthesis



Ocular Surface Stem Cell Transplant Advantages

- Can be used for severe conjunctival disease (symblepharon, conjunctival inflammation)
 - Where primary Kpro is not possible
- Easy IOP monitoring
- Improves and stabilizes ocular surface for subsequent keratoplasty
- Complications result in loss of surface only not loss of the eye
- Follow up can be reduced once surface stabilized



Ocular Surface Transplantation

Ideal patient

- ◇ Young, Middle age, or Older age in good overall health
- ◇ Able to comply with clinical and lab work follow-up, topical and systemic medications
- ◇ No contraindications to systemic immunosuppression
 - No history of malignancy < 5 years
 - No significant comorbidities: uncontrolled DM, uncontrolled HTN, renal insufficiency, CHF, organ failure
- ◇ Glaucoma controlled (tube shunt before OSST)
- ◇ Reasonable lid apposition (lid reconstruction before OSST)

Boston Type I KPro for Severe Ocular Surface Disease

Ideal Patient

Extent of Ocular surface disease

- Fornix intact and good ability to wear contact lens
- Good conjunctival function
- Absence of Severe Dry Eye
- Able to comply with frequent, *lifelong* follow up & topical medications
- No Severe Glaucoma
- Older patient



Lesson 11

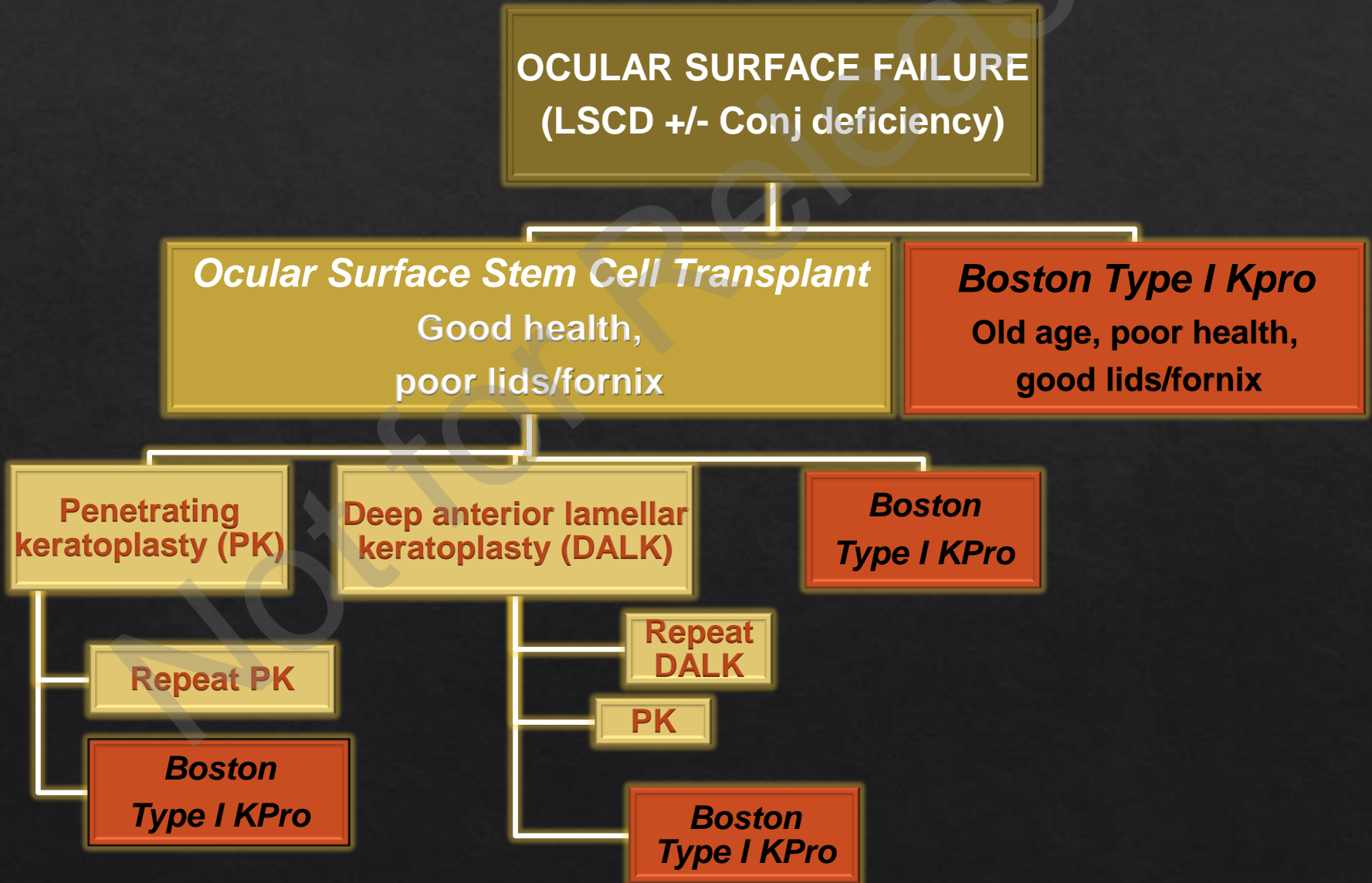
Ocular Surface Tx vs. Keratoprosthesis

*It is not “Which Technique is Better”
but rather*

“Which technique is best indicated for this patient”

- ◆ Both Ocular Surface Transplantation and KPro are successful methods for ocular surface reconstruction
- ◆ Specific indications and complications related to both procedures
- ◆ Surgeons should become accomplished with both procedures and the their complication management in order to offer Severe Ocular Surface Disease patients the best opportunity for visual recovery

Treatment Algorithm for Ocular Surface Reconstruction



Management of Severe Ocular Surface Disease: *Lessons Learned*

1. Do not perform Standard Keratoplasty
2. Ocular Surface Team is Critical to Success
3. Adopt Donor and Recipient Screening and IS Protocols from Organ Transplantation
4. Immunosuppression in OSST is Safe and Effective
5. “Staged Management” leads to Better Outcomes
6. Develop Treatment Paradigm Based on Stages of Severity
7. Good long term outcomes are possible with OSST for bilateral severe ocular surface disease

Management of Severe Ocular Surface Disease: *Lessons Learned*

8. OSST requires close monitoring
9. Incorporate KPro Surgery into the Treatment Paradigm
10. Boston KPros Have Complications
11. Ocular Surface Tx vs. Kpro -

It is not “Which Technique is Better” but rather “Which technique is best indicated for this patient”

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